Complete Summary

GUIDELINE TITLE

Human immunodeficiency virus (HIV). In: Sexually transmitted infections: UK national screening and testing guidelines.

BIBLIOGRAPHIC SOURCE(S)

Smit EJ. Human immunodeficiency virus (HIV). In: Ross J, Ison C, Carder C, Lewis D, Mercey D, Young H. Sexually transmitted infections: UK national screening and testing guidelines. London (UK): British Association for Sexual Health and HIV (BASHH); 2006 Aug. p. 101-9. [33 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Human immunodeficiency virus (HIV) infection
- Acquired immunodeficiency syndrome (AIDS)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Risk Assessment
Screening

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Urology

INTENDED USERS

Advanced Practice Nurses
Clinical Laboratory Personnel
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To provide advice on what tests for human immunodeficiency virus (HIV) infection are most appropriate in a United Kingdom (UK) genitourinary (GU) clinic setting
- To provide a basis for audit
- To support clinics when bidding for additional resources to meet national standards

TARGET POPULATION

All patients attending a genitourinary medicine (GUM) clinic in the United Kingdom

INTERVENTIONS AND PRACTICES CONSIDERED

1. Screening of symptomatic and asymptomatic patients for human immunodeficiency virus (HIV)
2. Use of Conformité Européenne (CE) marked HIV antibody tests
3. Interpretation of test results
4. Confirmation of positive HIV results
5. Specimens for testing (blood, urine, oral fluid, finger-stick blood)
6. Frequency of testing
7. Follow-up testing for cure

MAJOR OUTCOMES CONSIDERED

Sensitivity and specificity of test methods

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guidelines are based on all available scientific sources and where evidence is lacking, opinion of "best practices" by specialists in the field was used. Two main documents were consulted, the Centers for Disease Control and Prevention's (CDC's) "Revised guidelines for Human Immunodeficiency Virus (HIV) counselling, testing" (Nov 2001) and "Towards error free HIV diagnosis: guidelines on laboratory practice" produced by the Health Protection Agency (HPA) HIV Laboratory Diagnostic Forum. Publications from the CDC, HPA and Department of Health (DOH) were searched by means of their respective Internet search engines for keywords "HIV +/- guideline +/- testing." Likewise a Medline search was undertaken (November 2003) with the search criteria: "HIV + testing + guidelines" and the titles of the first 200 "hits" were reviewed of which 27 articles were selected for abstract review.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Ia: Evidence obtained from meta-analysis of randomised controlled trials

Ib: Evidence obtained from at least one randomised controlled trial

IIa: Evidence obtained from at least one well designed controlled study without randomisation

IIb: Evidence obtained from at least one other type of well designed quasi-experimental study

III: Evidence obtained from well designed non-experimental descriptive studies

IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The guidelines have been developed following the methodological framework of the Appraisal of Guidelines Research and Evaluation instrument (AGREE - adapted as described in *Int J STD and AIDS* 2004 15:297-305).

The extent to which the guideline represents the views of intended users has been addressed primarily by the authorship coming from the multidisciplinary membership of the Bacterial Special Interest Group (BSIG). As practising clinicians the authors were able to draw on their experience of applying the tests to symptomatic and asymptomatic patients, but it was not feasible to obtain formal input from representative patients.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Recommendations

A. Evidence at level Ia or Ib
B. Evidence at level IIa, IIb, or III
C. Evidence at level IV

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

After drafting, other health care professionals and professional bodies in genitourinary (GU) medicine were asked to comment, the draft guidelines posted on the British Association for Sexual Health and HIV (BASHH) website for 3 months, and all comments reviewed before final publication.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the level of evidence (**I-IV**) and grade of recommendation (**A-C**) are provided at the end of the "Major Recommendations" field.

Screening

All patients attending the genitourinary medicine (GUM) clinic should be offered a human immunodeficiency virus (HIV) test, according to the National Strategy for Sexual Health and HIV, as part of the initial screening for sexually transmitted infections. This does not mean that testing is restricted to new patients only and all re-presenting HIV negative patients should be offered and encouraged to have serological testing for HIV and syphilis following possible re-exposure.

Screening of symptomatic and asymptomatic patients attending GUM clinics for HIV is indicated for the following reasons: the benefits of early self-knowledge of HIV infection in controlling the spread of HIV infection are now recognised; there is also enough evidence through cohort studies that show that many people will reduce sexual and needle sharing risk behaviour after a diagnosis of HIV infection and similarly, those who are unaware of their HIV status, do not change their high risk behaviours; highly active anti-retroviral treatment (HAART) is an important contributor in reducing transmission due to the reduction in HIV burden and therefore infectivity in those individuals who are diagnosed early and treated; there is also consensus that it is best to start HAART before the onset of severe immunosuppression.

Screening of asymptomatic at risk groups is most effective if it is coupled with a personalised prevention counselling service. The screening service should provide information regarding the transmission, prevention, and the meaning of HIV test results. This information should form part of a leaflet that everybody should receive. Additional information should be offered to those declining testing as lack of perceived risk has been found to be the main reason for test refusal. Confidentiality of patients must be ensured and informed consent must be obtained beforehand according to the Department of Health (DOH) Guidelines for Pretest Discussion.

Recommended Tests

Only Conformité Européenne (CE) marked tests should be used for diagnostic purposes. There are a number of different HIV antibody tests available in the United Kingdom (UK) and all have similar sensitivities (99.78% to 100%) and specificities (99.5% to 99.93%) when they are performed according to the manufacturers specifications. Most laboratories use enzyme immunoassays (EIA) for screening although some of the rapid types of tests are also used for same day test results. A Clinical Pathology Accreditation (CPA) accredited laboratory should perform these tests and the specific test choice will be dictated by local circumstances. The screening assay should be able to detect both anti-HIV-1 and anti-HIV-2 antibodies (third generation test) and preferably p24ag (fourth generation test). Initial repeated screen positive tests should be referred to a specialist laboratory for confirmatory testing.

Interpreting Test Results

When interpreting test results the requesting physician should always remember that no diagnostic test is 100%, and although the tests have sensitivities and specificities close to 100%, false positive and false negative tests can still occur. Because the prevalence of HIV in the UK is very low, as a general rule low false

positive screening tests (negative on confirmatory tests) tend to occur, whilst false negative tests (unless a person is in the window period) are extremely rare.

Negative HIV Test Results

Patients whose specimens test non-reactive (negative) on the initial HIV screening assay should be regarded as non-infected unless the patient presents with symptoms of primary HIV infection (PHI) when it should be repeated after a week. (**Grade of Recommendation C, Evidence Level IV**)

If a recent exposure to an infected partner or partner of unknown HIV status has occurred within the previous three months, the patient may still be in the window period where HIV antibodies have not yet been produced, but p24 antigen (detected as part of the fourth generation or "combo" tests) and/or HIV ribonucleic acid (RNA) may test positive. Repeat testing after at least 3 months has lapsed since the exposure (see frequency of repeat testing below) should be performed. (**Grade of Recommendation C, Evidence Level IV**)

HIV seroconversion is detected in about 50% of cases about one month after exposure using third generation tests and three to four weeks after exposure using fourth generation tests.

Cases of prolonged or no seroconversion have rarely been reported. These initial reports were all tested with older generation antibody tests and many of these long window period cases tested HIV RNA negative on retesting, suggesting infection was caused by a re-exposure at a later date. It is therefore important to stress that the majority of the population will seroconvert within 3 months; however, repeated re-exposure is common and that can seemingly prolong the seroconversion period. In cases where post exposure prophylaxis (PEP) was given it will still be recommended that a 6 month follow-up period should be allowed to exclude the majority of seroconversions simply because of the lack of literature to prove otherwise and due to the fact that antiretrovirals may reduce replication and prolong antibody response. (**Grade of Recommendation C, Evidence Level IV**)

If a patient presents with clinical symptoms suggestive of HIV infection or acquired immunodeficiency syndrome (AIDS) and the HIV screening tests are repeatedly negative, then referral of the specimen to a specialist testing unit is recommended. (**Grade of Recommendation C, Evidence Level IV**)

Positive HIV Test Results

The approach in England and Wales is to employ at least two confirmatory HIV antibody tests following the initial reactive screening assay. The third confirmatory assay may or may not be a highly specific test such as a line immunoassay (LIA). This approach is recommended by the World Health Organisation and the underlying principal has been thoroughly substantiated.

It is important that the referral confirmatory laboratory distinguish between HIV-1 and HIV-2 infections. A positive diagnosis of HIV-2 can be made by means of a line immunoassay, Western blot (WB) or rapid test devices that incorporate

separate type-specific reaction spots. The GUM clinic should be aware if the referral laboratory is not able to distinguish between HIV-1 and HIV-2 infections, since the viral load assays and treatment need to be tailored for people with HIV-2 infections. Patients who are HIV positive and at risk of HIV-2 infections, such as those from Portugal or West Africa, should have their blood specimens sent to a laboratory that can make the distinction.

A second specimen for confirmation of HIV seropositivity always should be tested to exclude mislabelling and misidentification of the patient. (**Grade of Recommendation C, Evidence Level IV**)

Indeterminate and Unconfirmed HIV Test Results

The occurrence of false positive or non-specific reactions in the screening assays is not that uncommon, since most of the HIV screening is done in populations with a low prevalence (<1%). The usual scenario is that of a low positive signal (repeated twice) in a screening assay while the second and a third assay are negative. At this stage, if primary HIV infection is not suspected, patients should not be told that they are HIV positive but rather that a false positive reaction is most likely. A repeat blood sample should be sent to the laboratory for exclusion of seroconversion. In the interim period, the patient should refrain from unprotected sex that might put their partners at risk of infection. Most patients who are truly infected with HIV-1 will develop a confirmed HIV antibody positive profile within one month. However, evolving signals in the EIAs or evolution to specific HIV antigens in the WB/ LIA develop quickly in cases of seroconversion, and, therefore, an anxious patient can be reassured of a non-specific reaction after a repeat sample taken at least one week after the first sample if there is non-evolving serology. Once again, it is important to ensure that another follow-up blood is tested at least 3 months after the last exposure to exclude infections in the window period. (**Grade of Recommendation C, Evidence Level IV**)

In the cases where a test initially weakly reactive becomes strongly reactive in all of the confirmatory assays seroconversion can be diagnosed. At this stage, it is also common to detect p24 antigen that needs to be neutralised to increase specificity. At this stage, it should be decided whether to enrol the patient into the Medical Research Centre (MRC) seroconversion cohort or other available treatment studies.

Nucleic acid testing for HIV-1 RNA (viral load assay) or HIV-1 deoxyribonucleic acid (DNA) can help to distinguish non-specific reactions from seroconversion. A low level HIV viral load result may well be falsely positive in the situation of possible seroconversion. The caveat is that HIV-1 viral load assays are not validated for HIV diagnosis and it is best performed on a follow-up ethylene diamine tetraacetic acid (EDTA) blood sample.

GUM clinics that make use of same day testing should ensure that the patient is made aware of the fact that a delay in providing a test result on the same day does not, per definition, mean that the result is positive and that it happens not uncommonly.

Recommended Specimens for Testing

Blood (EDTA or clotted) is sent to the laboratory for anti-HIV-1 and 2 testing.

Other body fluids, such as urine, oral fluid and finger-stick blood, although routinely used in the other countries including the USA, have mainly been used for sero-epidemiological studies in the UK.

Rapid tests in order to provide a same day result service should preferably be performed in a local accredited laboratory and not on site in a GUM clinic.

Factors Which Alter Tests Recommended or Sites Tested

Due to a restraint of resources, a GUM clinic may not be able to comply with the DOH's sexual health directive to test all patients attending the clinic. In these circumstances priority should be given to the following risk groups:

1. Patients whose symptoms are compatible with acute retroviral illness or immunosuppression
2. Patients who practice unsafe sex (i.e., unprotected anal/vaginal sex with multiple partners) past/current history of sexually transmitted disease (STD), sexual assault
3. Patients who are known contacts of HIV infected patients
4. Intravenous drug users (IVDUs) who share "equipment"
5. Patients who come from countries with a high HIV prevalence
6. Patients who travel abroad with exposure to high risk activity

Recommendation for Frequency of Repeat Testing in an Asymptomatic Patient

(**Grade of Recommendation C, Evidence Level IV**)

A positive test should be followed up by a repeat HIV test to exclude the possibility of a specimen mix-up.

A negative test cannot exclude a recent infection if the exposure was less than 3 months ago (*see interpretation of tests above*).

The timing and frequency of retesting has not yet been firmly established.

The following factors should be taken into consideration when recommending follow-up testing:

1. Timing of last potential exposure. If it is thought that a recent possible exposure has happened, then a patient with a negative test should undergo a repeat test in at least three months' time.
2. Probability of HIV infection given type of exposure. Patients who have had a definite HIV exposure and in those cases where post exposure prophylaxis was given, need follow up at three and six months.
3. Ongoing high-risk behaviour. One of the aims of counselling is to modify high risk behaviour, but if there is continuation then frequent testing would be advocated.

4. Patients who are very anxious might be retested sooner following an indeterminate test result (i.e., after one week) – *see under indeterminate results above*.
5. When a patient presents again to a GUM clinic then per definition they should be treated as a new patient and be retested for HIV.

Recommendation for Test of Cure

There is no test of cure, but all HIV antibody positive patients should be referred on to a specialist HIV treatment and care centre for further HIV-1 viral load testing and management. It is important to make sure that the referral laboratory stores all HIV viral load plasma indefinitely for future retrospective resistance testing should the need arise.

Definitions:

Levels of Evidence

Ia: Evidence obtained from meta-analysis of randomised controlled trials

Ib: Evidence obtained from at least one randomised controlled trial

IIa: Evidence obtained from at least one well designed controlled study without randomisation

IIb: Evidence obtained from at least one other type of well designed quasi-experimental study

III: Evidence obtained from well designed non-experimental descriptive studies

IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grading of Recommendations

A. Evidence at level Ia or Ib
B. Evidence at level IIa, IIb, or III
C. Evidence at level IV

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate screening and diagnosis of human immunodeficiency virus (HIV) infection

POTENTIAL HARMS

When interpreting test results the requesting physician should always remember that no diagnostic test is 100%, and although the tests have sensitivities and specificities close to 100%, false positive and false negative tests can still occur.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Special mention on the 3 month follow-up post sexual exposure should be made. The Centers for Disease Control and Prevention's (CDC's) guidelines states that following a sexual exposure a six month follow-up period should be allowed to exclude human immunodeficiency virus (HIV) infection. The Health Protection Agency (HPA) guidelines do state that at least six months needs to pass following a needle stick injury to exclude infection, a period also accepted in these guidelines. However, following sexual exposure, the HPA guidelines are not clear whether the recommendation of "testing immediately after the exposure and then: at one to two months, at three to four months and six months" only pertains to needle stick injuries or also to sexual exposures.

As mentioned in these guidelines, the six months waiting period is based on some pivotal old studies that used "known" exposure dates to calculate seroconversion periods. From a review of data from one of the most reliable of these studies and other data, a conclusion was drawn that states that seroconversion in a third generation assay would, in about 50% of cases, occur one month after exposure and four to eight days earlier using a fourth generation assay. The drawback from the other studies were that they were performed when less sensitive (first and second generation) tests were used; it was not taken into account that most people will only seroconvert following repeated sexual exposures and retesting initial polymerase chain reaction (PCR) test positive samples did not confirm the results. This can be explained by the fact that initial PCR reactions were crude and gave many false positive reactions, which meant that the infected patients most probably got infected at a much later stage when they were re-exposed to HIV.

At the Birmingham HPA laboratory, clinicians have employed an "at least" 3 month follow-up period after the last sexual exposure for a few years and they have not had any known patients seroconverting beyond this time period. Dr Philip Mortimer, Ex-Director Sexually Transmitted & Blood Borne Virus Laboratory, HPA is also not aware of any seroconversion beyond 3 month exposure cases, and he is of the opinion that the three month follow-up period is perfectly reasonable following a sexual contact (personal communication).

Selecting the phrase "at least" 3 months follow-up also does not go against the Department of Health guidelines for pre-test discussion that states: "If thought a recent possible exposure, a patient could be in the window period they should be advised to undergo a repeat test in three to six month's time."

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Smit EJ. Human immunodeficiency virus (HIV). In: Ross J, Ison C, Carder C, Lewis D, Mercey D, Young H. Sexually transmitted infections: UK national screening and testing guidelines. London (UK): British Association for Sexual Health and HIV (BASHH); 2006 Aug. p. 101-9. [33 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Aug

GUIDELINE DEVELOPER(S)

British Association for Sexual Health and HIV - Medical Specialty Society

SOURCE(S) OF FUNDING

No specific or external funding was sought or provided in the development of this guideline.

GUIDELINE COMMITTEE

Screening Guidelines Steering Committee
Clinical Effectiveness Group (CEG)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Author: Dr EJ Smit, Birmingham

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr EJ Smit does not have any personal interests or conflicts of interest to be declared.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from British Association for Sexual Health and HIV Web Site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Specifications for the development of UK guidelines on the management of sexually transmitted infections (STIs) and closely related conditions 2005. London (UK): British Association of Sexual Health and HIV (BASHH); 2005. 14 p. Electronic copies: Available in Portable Document Format (PDF) from the British Association for Sexual Health and HIV Web site.

Additionally, auditable outcome measures can be found in the original guideline document.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on June 26, 2008. The information was verified by the guideline developer on October 20, 2008.

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Date Modified: 11/10/2008


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